

# Nicotine Mouth Spray, 1 mg

**Nonprescription Drugs Advisory Committee**

September 18, 2019



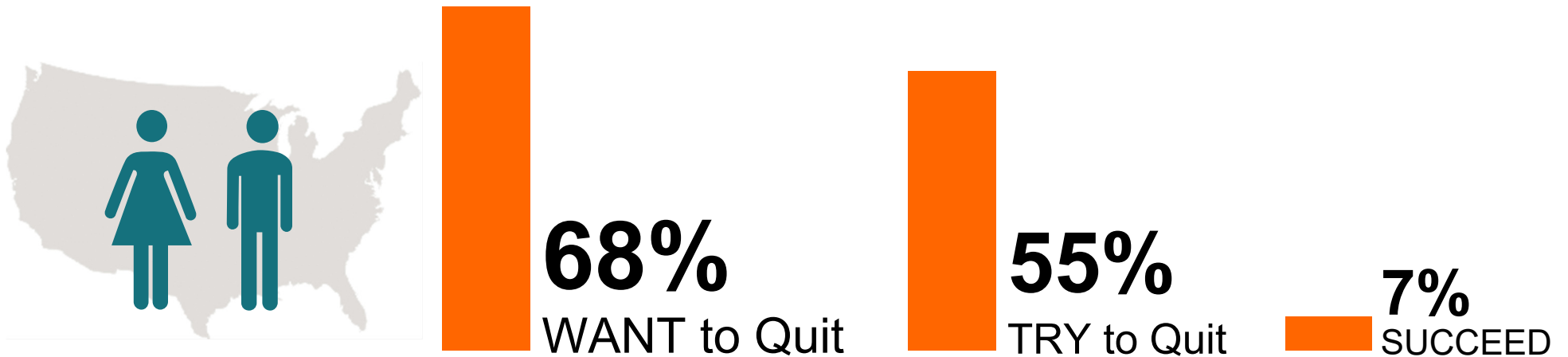
# Introduction

**Sue James**

Vice-President, Head Global Regulatory Affairs

# Smoking is Still a Significant Public Health Issue

**34 MILLION** Americans continue to smoke | **~ 500,000 DEATHS** each year



## NRT

First-line, evidence-based medication to help people to quit smoking by reducing their withdrawal symptoms

# There is Substantial Market History with NRT

## Rx Only

RX  
2mg Gum

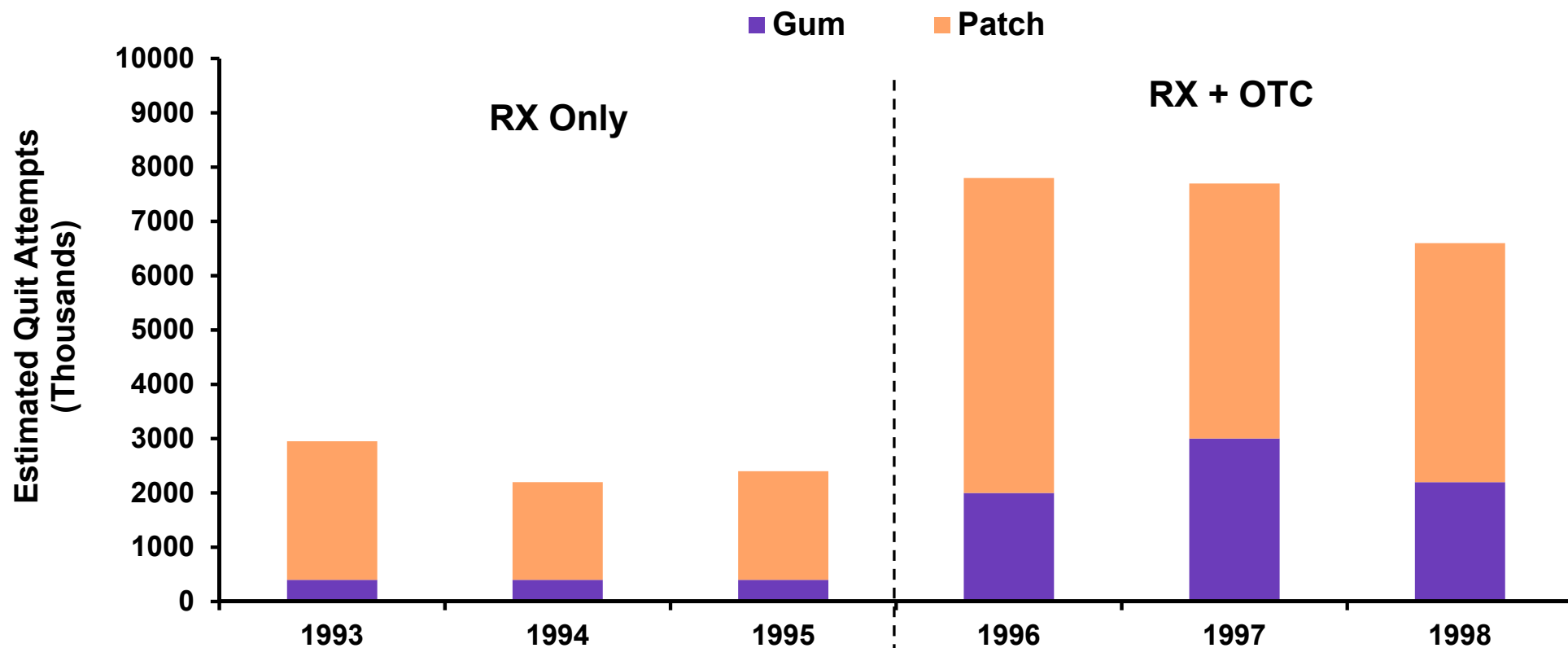
RX  
4mg Gum

RX  
Patch

## OTC



# OTC NRT Access Increased Quit Attempts



# The Need For NRT Innovation

- **FDA's 2017 call to action**
  - Encourage NRT innovation
  - Promote development of novel nicotine delivery systems
  - Ensure policies encourage development of NRT innovation
- **Nicotine Mouth Spray (NMS) is a novel, differentiated dose form**
  - Flexible dosing based on the consumer's urge to smoke

# Nicotine Mouth Spray is an Important Innovation



# NMS Has Significant Market History and Exposure

**Total ex-US Markets Where NMS is Approved as a Nonprescription Product**



# NMS Development Program Meets 2019 FDA Guidance

## FDA Development Requirements

PK Data



Efficacy Trial(s)



Actual Use Efficacy Trial



Label Studies



## NMS Development Program

- 4 PK studies (single-dose, multiple dose)
- 1 PD study to evaluate urge to smoke

- 52-week efficacy and safety study (“Standard”)

- 26-week efficacy and safety study (“Naturalistic”)

- 4 label comprehension studies
- 3 human factors studies

## NMS is Differentiated from other Oral NRT

- **NMS nicotine absorption profile**
  - Faster time to maximal nicotine plasma concentration
  - Higher concentrations of nicotine immediately after dosing
- **Positive effect on the relief from nicotine withdrawal symptoms, including cravings**

## NMS has a Well-established Safety Profile

- **Significant exposure**
  - Significant clinical safety experience with NMS
  - Significant post-marketing safety experience with NMS
- **Similar adverse events profile to oral NRT**

## Abuse is Unlikely

- **Adolescent abuse raised as a concern by FDA in 1996 for the gum and patch**
- **GSK undertook a comprehensive Phase IV study for 6 years**
- **NMS abuse is unlikely**
  - Absorption is lower/slower than inhaled nicotine (cigarettes)
  - Phase IV data on gum and patch are reassuring
  - Postmarketing safety data from ex-US on NMS does not show any new safety signals

## NMS is Effective

- **Two pivotal trials:**
  - **Standard Efficacy Trial** – with instruction and verbal behavioral support
  - **Naturalistic Efficacy Trial** – with OTC labeling only
- **Both met primary endpoint(s)**
- **Behavioral support helps to achieve higher absolute quit rates**
- **Both pivotal trials achieved doubling of quit rates**

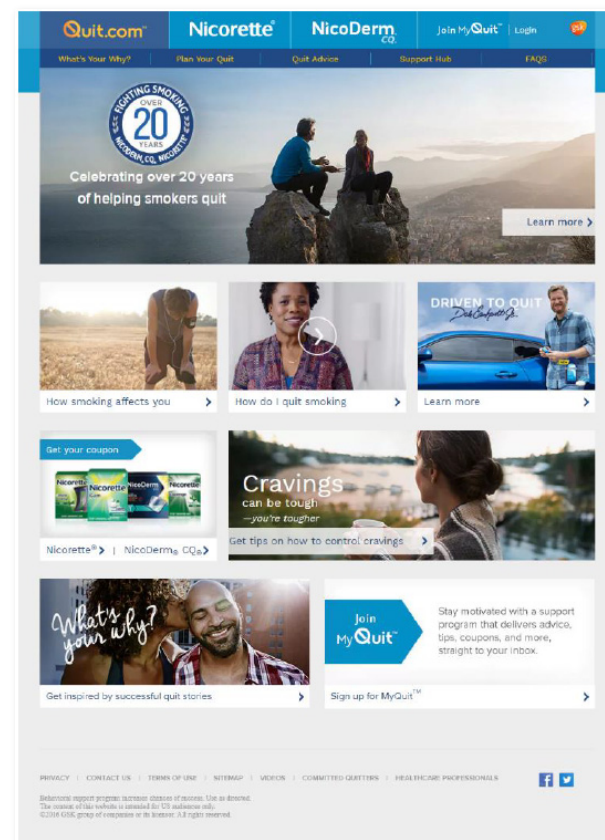
# **Consumers Can Understand the Labeling and Know How to Use the Product**

- **Consumers demonstrated comprehension of unique NMS label statements**
- **Consumers demonstrated that they could use the device based on product labeling**
- **Consumers understood key motivational messages within the product User's Guide**

# GSK is Committed to Enhancing Consumer Experience

## Plans for Holistic Consumer Support

- Simple, engaging self-help materials (Quick Start Guide and User's Guide)
- MyQuit Behavioral Support Program
- Access to variety of behavioral self-help tools
- Website-hosted demonstrative videos
- 1-800 number



# Agenda

<b>Introduction</b>	<b>Sue James</b> <i>Vice President, Regulatory Affairs, GSK</i>
<b>Efficacy Review</b>	<b>Mitch Nides, Ph.D.</b> <i>President, Los Angeles Clinical Trials</i>
<b>Real-World NRT Effectiveness</b>	<b>John Hughes, MD</b> <i>Professor, Center for Health and Behavior Departments of Psychiatry and Psychological Sciences University of Vermont</i>
<b>Safety Review</b>	<b>Raj Mishra, MD</b> <i>Global Vice President, Medical Affairs, J&amp;J</i>
<b>Consumer Studies Review</b>	<b>Julie Aker</b> <i>President &amp; CEO, Concentrics Research</i>
<b>Benefit-Risk Summary</b>	<b>Sue James</b> <i>Vice President, Regulatory Affairs, GSK</i>

## Additional Responders

<b>Scott Leischow</b>	<b>External Consultant, Professor and Director, Translational Sciences, Arizona State University</b>
<b>David Schiffkovitz</b>	<b>External Consultant, former GSK VP Regulatory</b>
<b>Andrew Myers, MD</b>	<b>J&amp;J Senior Director, Head of Clinical Research</b>
<b>Erin Oliver, MS, MBA</b>	<b>GSK Senior Director, Global Regulatory Lead</b>
<b>Anna Hansson, M.Sc.</b>	<b>J&amp;J Clinical Pharmacology</b>
<b>Thomas Jaeger, MD</b>	<b>J&amp;J Director, Medical Safety Officer</b>
<b>Ken Christensen, MBA</b>	<b>GSK Marketing Director, U.S. Smokers' Health</b>

# Efficacy Review

**Mitchell Nides, Ph.D.**

President, Los Angeles Clinical Trials

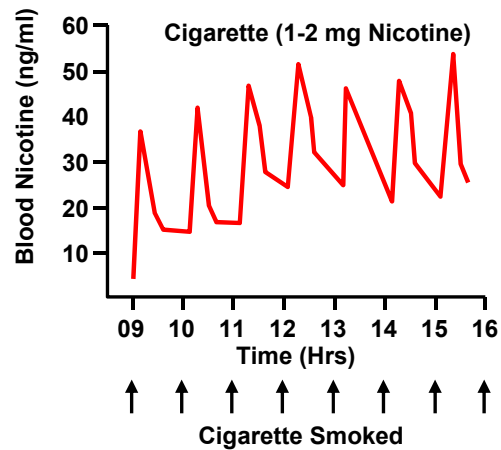
# Outline of Efficacy Review

- **The Science of Addiction & Mechanism of NRT**
- **PK/PD Development Rationale**
- **Pivotal Efficacy Data**

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# Why is it So Hard to Quit Smoking?



**Physiologic**



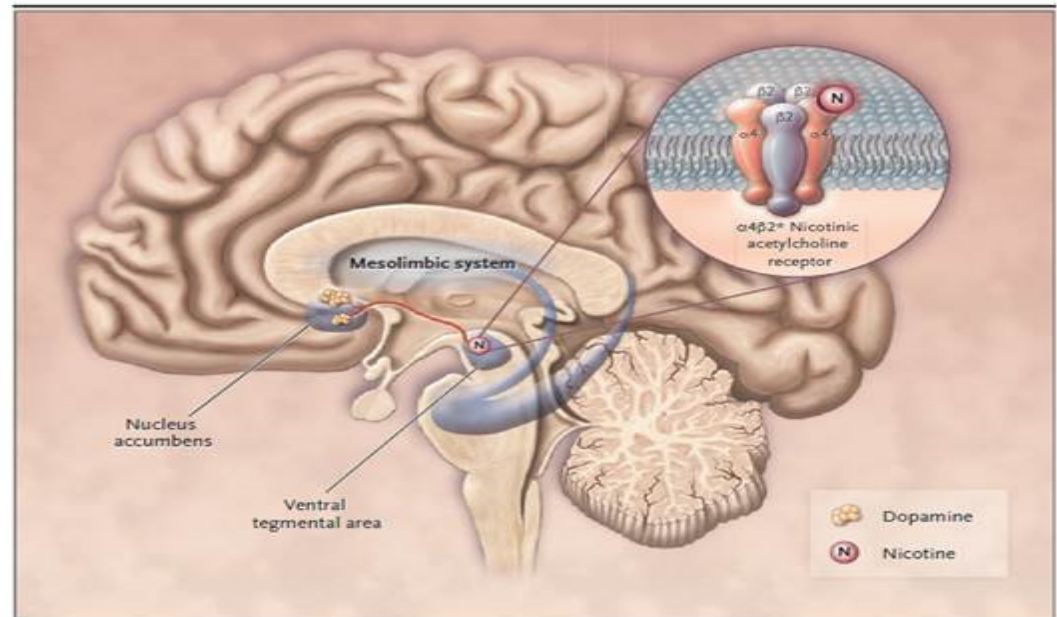
**Psychologic**



**Behavioral**

# How Nicotine Addiction Works

- 10 seconds for nicotine from one puff from a cigarette to reach the brain
- Nicotine stimulates release of dopamine – leading to pleasurable CNS effects



## Role of the Mesolimbic Dopamine System in Nicotine Activity

Nicotine activates  $\alpha 4 \beta 2$  receptors in the ventral tegmental area, resulting in dopamine release in the shell of the nucleus accumbens

# Nicotine Withdrawal and The Role of NRT

- **Short half-life leads to withdrawal symptoms:**
  - Urge to smoke
  - Irritability
  - Difficulty concentrating
  - Mood swings
  - Sleep disturbances
  - Increased appetite
- **Strong cravings and withdrawal symptoms lead to relapse**
- **NRT designed to “replace” nicotine and reduce withdrawal symptoms**

# Providing Different NRT Options is Important

- All forms of NRT have been proven effective
- Consumers choose which form best suits their individual need

## NRT Transdermal Patch

- Once-a-day sustained craving relief
- Reduces background craving

## NRT Gum

- Acute craving relief
- 2 mg/4 mg based on individual need

## NRT Lozenge/Minis

- Acute craving relief
- 2 mg/4 mg based on individual need
- For those who don't chew gum

## NRT Mouth Spray

- Acute craving relief
- Fast onset of action and flexible dosing based on urge to smoke

# NMS Dosing is Flexible Based on Urge to Smoke

NRT Format	Directions	Step 1 Weeks 1-6	Step 2 Weeks 7-9	Step 3 Weeks 10-12
Gum	"Chew and park" for 30 min			
Lozenge	Place in mouth and allow to slowly dissolve while occasionally moving around mouth (about 30 min)	1 piece every 1-2 hours	1 piece every 2-4 hours	1 piece every 4-8 hours
Mini Lozenge	Place in mouth and allow to slowly dissolve (about 10 min)			
NMS	Spray in mouth when urge to smoke	1-2 sprays; max 4 sprays per hour	Reduce by half	Reduce more; max 4 sprays per day by week 12

# Outline of Efficacy Review

- The Science of Addiction & Mechanism of NRT
- **PK/PD Development Rationale**
- Pivotal Efficacy Data

# Pharmacokinetic/Pharmacodynamic Rationale for NMS

- **Faster nicotine delivery may lead to faster craving and withdrawal relief**
- **Nicotine from NMS is more quickly absorbed into the oral mucosa**
  - Nicotine in solution is more readily available vs. gum and lozenge
  - Spray allows for more immediate release vs. solid dose forms dissolving over 10-30 minutes

**Step 1:** Nicotine migration from gum/lozenge

**Step 2:** Dissolution into saliva

**Step 3:** Absorption into mucosa



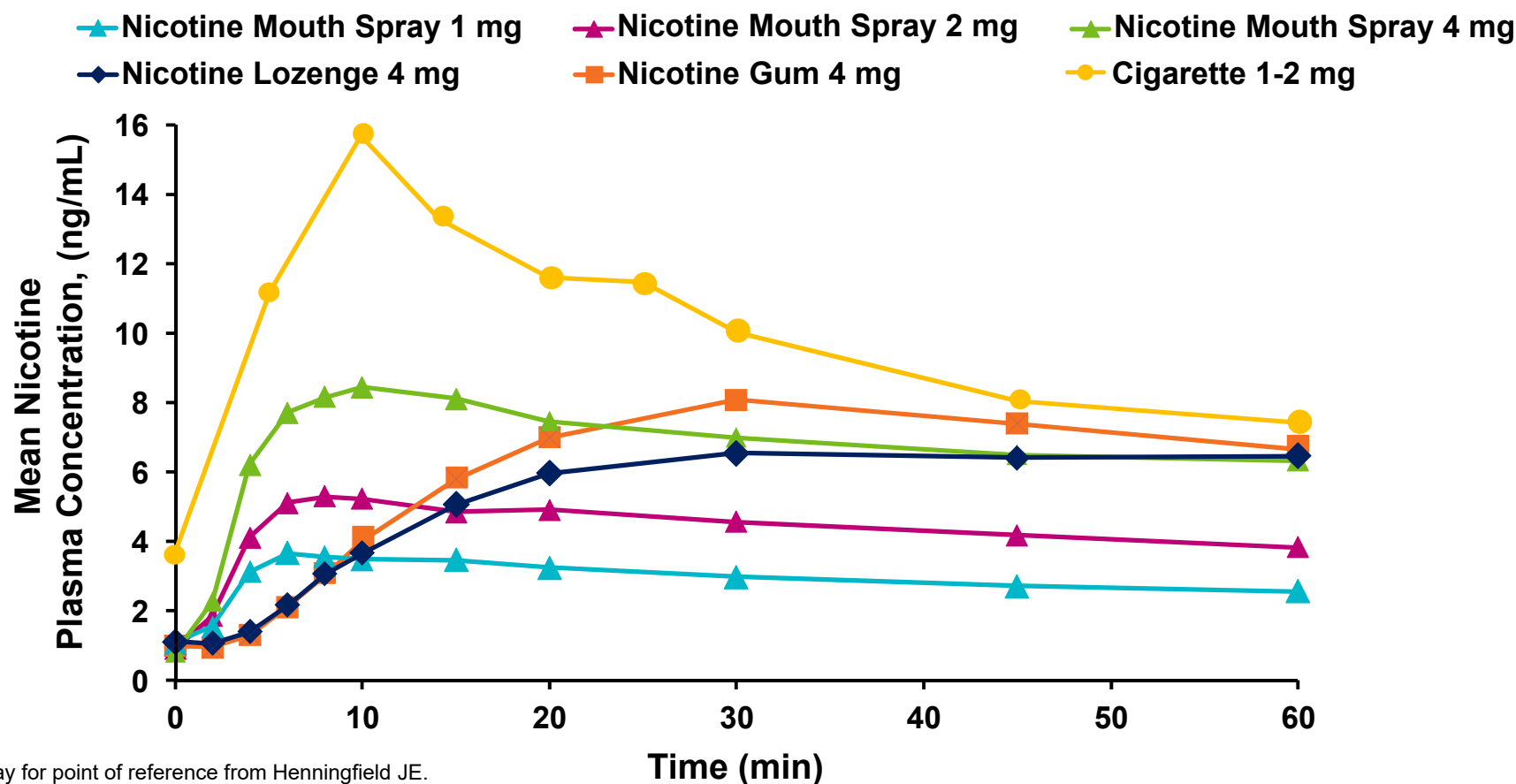
**Direct Absorption  
of Solution**



# Extensive NMS Pharmacology Program

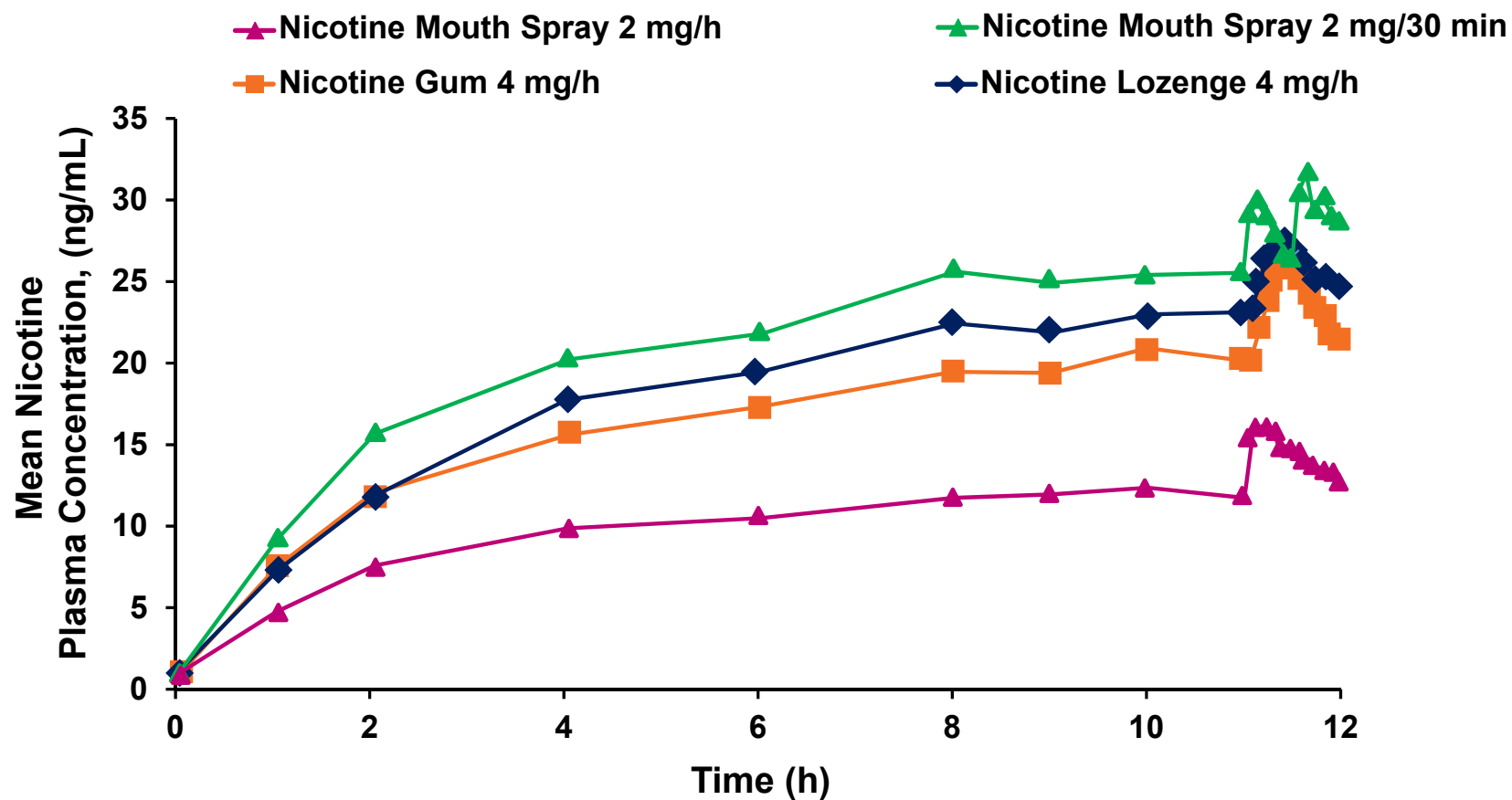
- **4 pharmacokinetic studies**
  - **PK Study 1094:** Spray location in mouth does not greatly affect absorption
  - **PK Study 1107:** No impact of 20 second delay between doses
  - **PK Study 1065:** NMS PK profile vs gum and lozenge over 12 hours
  - **PK Study 1066:** NMS PK profile vs gum and lozenge over 60 minutes
- **1 pharmacodynamic study (PD Study 2011)**
  - Assessed urge to smoke
- **Total of 340 subjects**

# PK Profile Demonstrates More Rapid Absorption

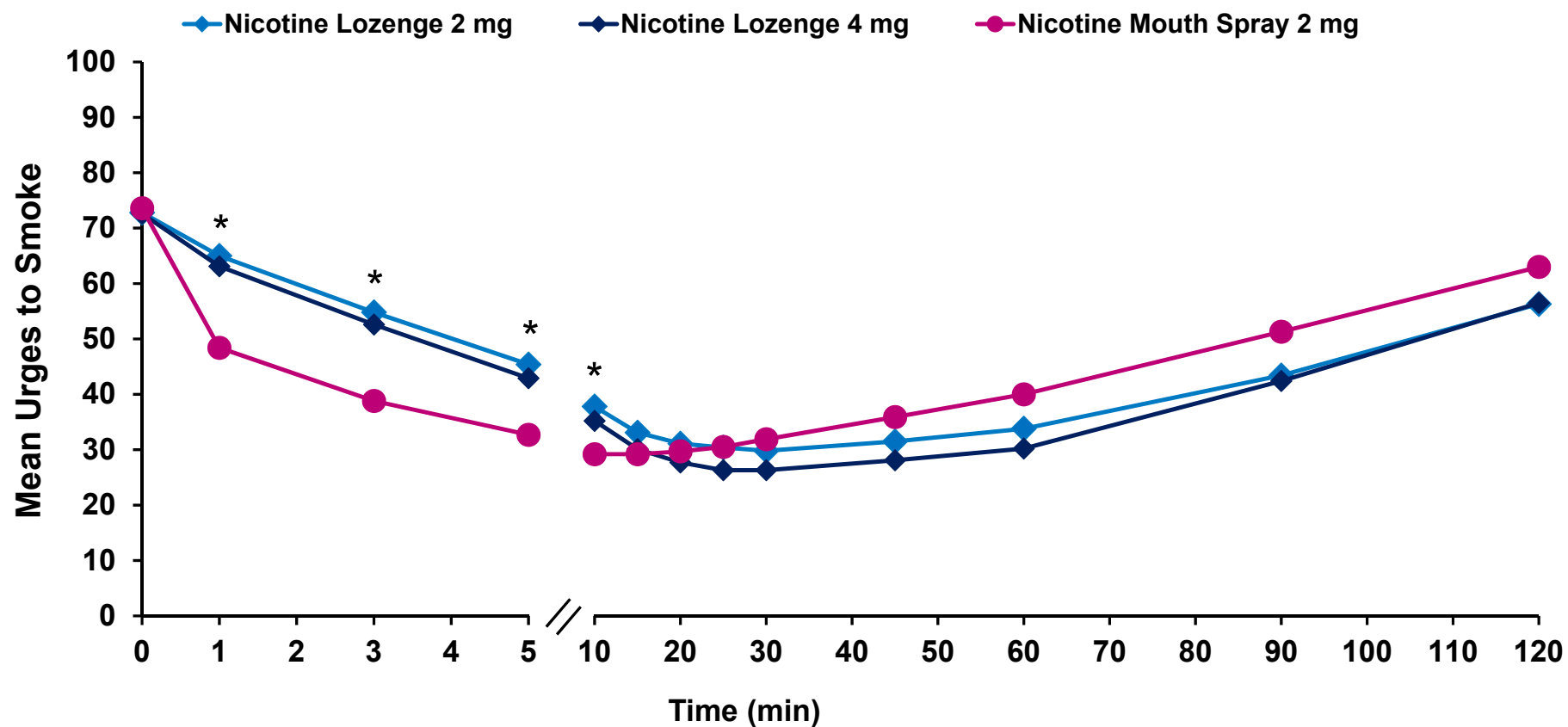


Cigarette overlay for point of reference from Henningfield JE.  
NEJM. 1995;333:1196-1203

# PK Profile Shows Comparable Extent of Absorption



# PD Data Shows Greater Reduction in Craving Through First 10 minutes



Mean urges to smoke vs. time curve during 120 min post-administration. Note: change in scale from 5 min onwards

\* Indicates a statistically significant difference ( $p < 0.001$ )

# Outline of Efficacy Review

- The Science of Addiction & Mechanism of NRT
- PK/PD Development Rationale
- **Pivotal Efficacy Data**

## Two Types of Trials in NMS Pivotal Program

- **A “standard” efficacy trial**
  - Required instruction by trial staff on product use
  - Verbal behavioral support and counseling for all subjects
  - Provides evidence of product efficacy
- **A “naturalistic” efficacy trial**
  - NO training on how to use the drug product provided by the trial staff
  - NO verbal behavioral support
  - Provides evidence that consumers can use the drug product successfully in an OTC environment without guidance

# Study Design – Pivotal Trials

**Both studies were double-blind, parallel group studies**

<b>Study Design Characteristics</b>	<b>Standard Efficacy Study 11</b>	<b>Naturalistic Efficacy Study 38</b>
<b>Timeframe</b>	<b>2009 - 2010</b>	<b>2015 - 2016</b>
<b>Length of Study</b>	<b>52 weeks</b>	<b>26 weeks</b>
<b>Location of Study</b>	<b>EU</b>	<b>US</b>
<b>Number of Subjects</b>	<b>479 enrolled 242 completed</b>	<b>1198 enrolled 717 completed</b>
<b>Primary Endpoints</b>	<b>Continuous CO-verified smoking cessation from Week 2 to Weeks 6 (and 24, and 52)</b>	<b>Continuous CO-verified smoking cessation from Week 2 to Week 6</b>

# Other Design Variables that Influence Outcome

<b>Design Variables</b>	<b>Standard Efficacy Trial</b>	<b>Commit Lozenge</b>	<b>Naturalistic Efficacy Trial</b>
<b>Verbal Instructions on Product Use</b>	<b>Yes</b>	<b>Yes</b>	<b>No</b>
<b>Verbal Behavioral Support</b>	<b>Yes Baseline (&lt;10 min) Each visit (&lt;3 min)</b>	<b>Yes Baseline (5 -10 min) 1<sup>st</sup> 4 visits (5-10 min)</b>	<b>No</b>
<b>Label Warning – No use while smoking</b>	<b>Yes</b>	<b>Yes</b>	<b>No</b>
<b>Quit Day</b>	<b>Directed to quit next day</b>	<b>Directed to quit next week</b>	<b>Encouraged to quit next day</b>

# Results of Standard Efficacy Trial Study 11

	NMS N=318 n (%)	Placebo N=161 n (%)	OR (95% CI) <sup>a</sup>	p-value <sup>b</sup>
<b>2-6 Weeks</b>	<b>83 (26.1)</b>	<b>26 (16.1)</b>	<b>1.83 (1.12-2.99)</b>	<b>0.014</b>
<b>2-12 Weeks</b>	<b>64 (20.1)</b>	<b>21 (13.0)</b>	<b>1.68 (0.98-2.87)</b>	<b>0.055</b>
<b>2-24 Weeks</b>	<b>50 (15.7)</b>	<b>11 (6.8)</b>	<b>2.54 (1.28-5.04)</b>	<b>0.006</b>
<b>2-52 Weeks</b>	<b>44 (13.8)</b>	<b>9 (5.6)</b>	<b>2.71 (1.29-5.71)</b>	<b>0.007</b>

a Mantel-Haenszel statistics for the success OR, corresponding 95% CI  
b p-value of difference between the treatment groups based on Chi-square test

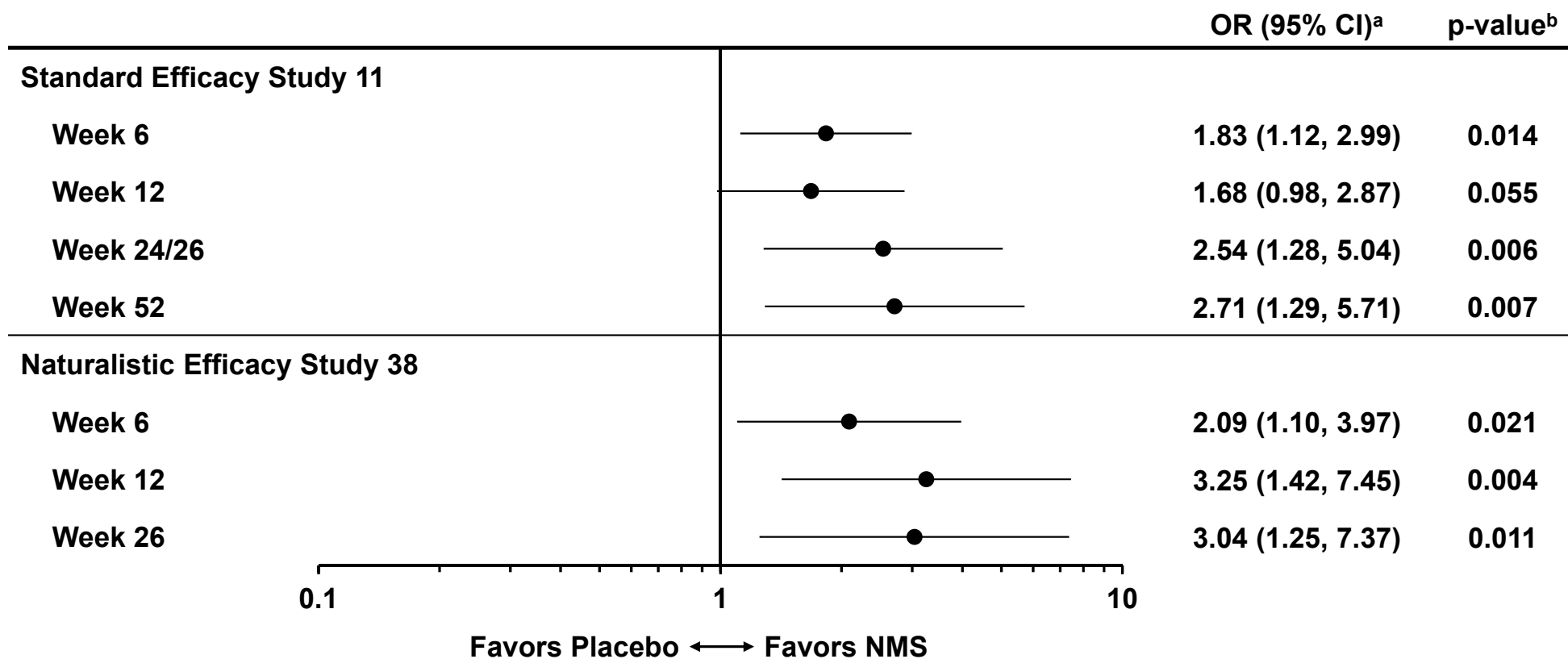
# Results of Naturalistic Efficacy Trial Study 38

	NMS N=597 n (%)	Placebo N=601 n (%)	OR (95% CI) <sup>a</sup>	p-value <sup>b</sup>
2-6 Weeks	30 (5.0)	15 (2.5)	2.09 (1.10-3.97)	0.021
2-12 Weeks	24 (4.0)	8 (1.3)	3.25 (1.42-7.45)	0.004
2-26 Weeks	20 (3.4)	7 (1.2)	3.04 (1.25-7.37)	0.011

<sup>a</sup> The 95% CIs for the OR were calculated with the normal approximation.

<sup>b</sup> p-value of difference between the treatment groups based on Cochran-Mantel-Haenszel test, stratified for study site and number of cigarettes smoked per day at baseline (<20 vs. ≥20 per day).

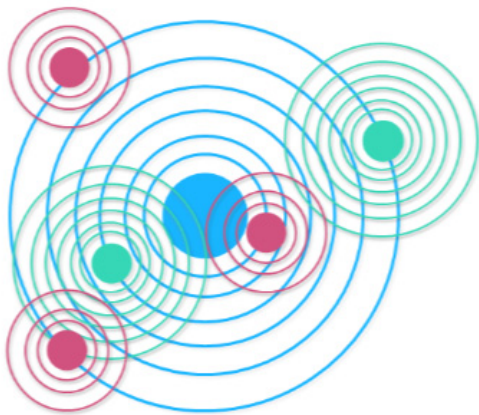
# Both Trials Show NMS Doubles Quit Rate



<sup>a</sup> OR calculated by Mantel-Haenszel statistics for the success OR, and normal approximation for corresponding 95% CI in the standard efficacy and naturalistic trials.  
<sup>b</sup> p-values between treatment groups were calculated by Chi-square test in the standard efficacy study and by the Cochran-Mantel-Haenszel test in the naturalistic study

# The Long-term Positive Cascade Effect of Quitting

- **A single quit can have a cascading effect further reducing the overall prevalence of smoking**



- **An individual's quitting smoking can directly influence the behaviors of those within their circle**
  - Reducing health consequences of 2nd and 3rd hand smoke
  - Encouraging the quit attempts of others by their success
  - Dissuading the start of smoking in children

## NMS has Proven Efficacy

- **Efficacy of NMS was demonstrated**
  - Standard efficacy trial and naturalistic trial designs
- **Results were statistically significant for the primary endpoint**
  - Continuous abstinence at week 6
- **Results achieved doubling of quit rates**
- **NMS is a new dosage form that offers a faster rate of nicotine delivery and different approach to dosing, based on the individual smoker's need**

# Real-World NRT Experience

**John Hughes, MD**

Professor Emeritus

University of Vermont College of Medicine

# Outline of Real-World NRT Experience

- 1. NRT doubles quit rates in standard efficacy trials**
- 2. NRT doubles quit rates in naturalistic efficacy trials**
- 3. Point prevalence is a useful measure of abstinence**
- 4. Small effect sizes have public health significance**

# NRT Doubles Quit Rates in Standard Efficacy Trials

	Quit Rate		
	Control	NRT	RR
Gum	10.0%	16.3%	1.5
Tablet/Lozenge	12.9%	21.0%	1.5
Patch	9.4%	15.7%	1.6
Inhaler	9.1%	17.0%	1.9
Intranasal Spray	11.8%	23.9%	2.0
Oral Spray	5.6%	13.8%	2.5
Choice of NRT	13.8%	18.0%	1.4

**6-14%**

**14-24%**

**1.5-2.5x**

RR=Relative Risk  
Cochrane Meta-analysis of 131 trials  
Hartmann-Boyce J, et al. Cochrane  
Database Syst Rev. 2018;5:CD000146.

# NRT Doubles Quit Rates in Naturalistic Efficacy Trials

	Quit Rate		
	Control	NRT	RR
Lozenge [Nelson 2019]	3.7%	7.5%	2.0
Patch [Cunningham 2016]	0.8%	2.4%	3.0
Patch [Davidson 1998]	5.5%	12.0%	2.2
Patch [Hays 1999]	5.9% 5.9%	7.2% blinded 10.8% open label	1.2 1.8
	<1-6%	2-12%	1.2-3.0x

## **Study Methods Establish Base Quit Rate**

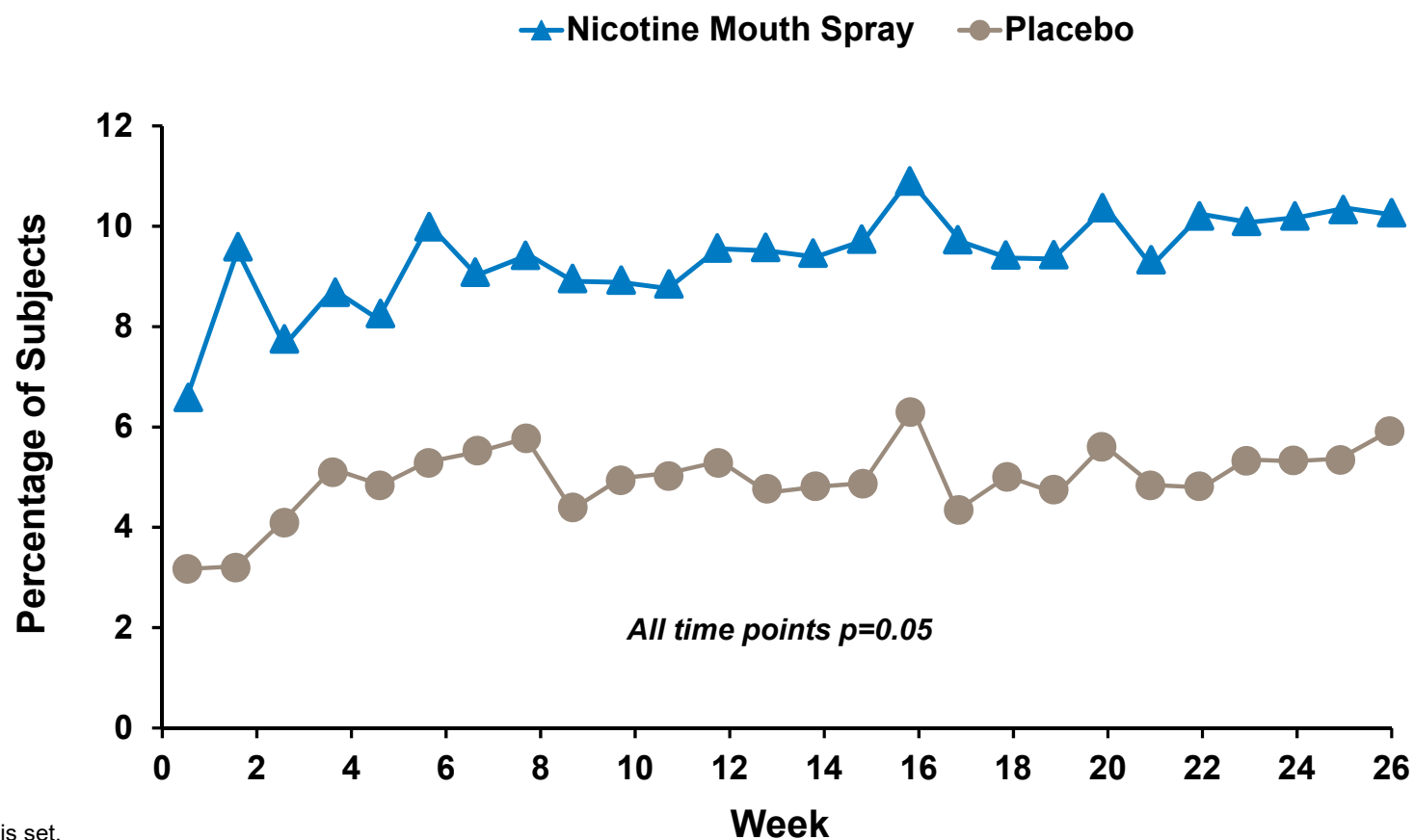
- **Study methods set the base rate and treatments have a multiplicative effect**
- **The absolute rate of quitting is due as much to study conditions as the drug effect**
- **The pharmacologic effect of the drug is the same in both standard and naturalistic studies**

# Two Different Measures of Smoking Abstinence

- **Continuous abstinence**
  - No smoking for several weeks or months
  - Not even a puff
  - Slips or delayed abstinence considered failure
- **7-day point prevalence**
  - Measures abstinence over previous 7 days
  - Allows for slips or delays on the way to quitting
  - Reflective of real-life behaviors because it takes many attempts to quit

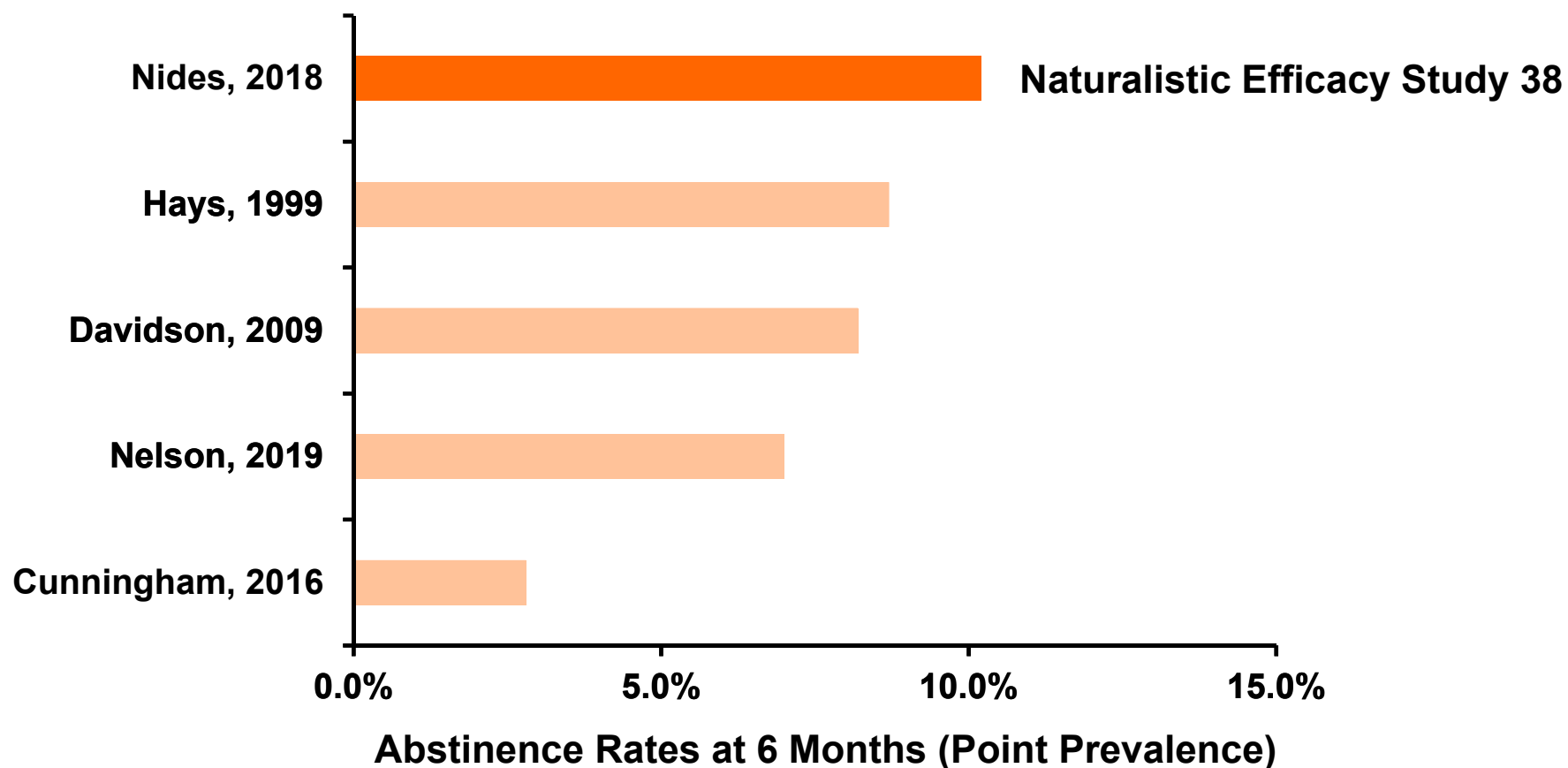
# Verified 7-Day Point Prevalence Abstinence

## Naturalistic Efficacy Study 38



Subjects in full analysis set.  
Nides M, et al. *Nicotine Tob Res.* Epub 2018 Nov 18.

# Point Prevalence Quit Rates in NRT Naturalistic Efficacy Trials are Similar



## **Small Effect Sizes Have Public Health Significance**

- **Many tobacco control activities result in increases less than 10%**
- **The UK National Institute for Health and Clinical Excellence considers small increases in treatment are worthwhile**

# NNTs Compare Favorably to Other Treatments

- **NMS for smoking abstinence**
  - 40 (naturalistic efficacy trial)
  - 10 (standard efficacy trial)
- **NNT to prevent a heart attack**
  - Thrombolytics = 43
  - Antihypertensive medications = 100
  - Statins = 104

# Summary

- **Small quit rates are due to study methods not low efficacy**
- **NRT doubles quit rates under standard and naturalistic conditions**
- **Both continuous abstinence data and point prevalence data show efficacy**
- **Smoking is so deadly that small increases in quitting have public health significance**

# Safety Review

**Rajesh (Raj) Mishra MD, PhD**

Vice President Global Medical & Clinical Sciences  
Johnson & Johnson Consumer Inc.

# **Outline of Safety Review: Nicotine Mouth Spray**

- 1. Safety experience of all Nicotine Replacement Therapy (NRT)**
- 2. Clinical safety experience with Nicotine Mouth Spray (NMS)**
- 3. Post-marketing safety experience with NMS (2011-2018)**
- 4. Specific safety considerations relevant to OTC use of NMS**

# Outline of Safety Review: NRT

- 1. Safety experience of all Nicotine Replacement Therapy (NRT)**
2. Clinical safety experience with Nicotine Mouth Spray (NMS)
3. Post-marketing safety experience with NMS (2011-2018)
4. Specific safety considerations relevant to OTC use of NMS

# Safety Profile is Well Established

- Clinical experience in **110+ trials**
- **Four decades** of post-marketing use
- More than **two decades** of use as an OTC smoking cessation aid
- **Global NRT exposure:** from 2008-2018, (all formulations) is **22 billion units\***
- **Global Nicotine Mouth Spray** exposure from 2011-2018:
  - **21.3 million units**
  - **>3 billion sprays**

\*Various strength; exposure estimation, not all countries, incl. data from business partners; Data from 23 countries available

# Outline of Safety Review: Nicotine Mouth Spray

1. Safety experience of all Nicotine Replacement Therapy (NRT)
- 2. Clinical safety experience with Nicotine Mouth Spray (NMS)**
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4. Specific safety considerations relevant to OTC use of NMS

## More than 1500 People Exposed to NMS in Clinical Development

- **140 exposed** in four Phase 1 pharmacokinetic studies
- **200 exposed** in a single-dose Phase 2 craving relief study
- **256 exposed** in a single-dose Phase 2 fixed vs flexible dose usage pattern study
- **915 exposed** in two long-term Phase 3 studies

## **Phase 1 and Craving Studies Revealed Higher Frequency of Hiccups and Local Reactions**

- **4 of 5 studies had a comparator NRT**
- **Generally AEs similar to comparator NRT except for higher frequency of**
  - Hiccups
  - Throat irritation
  - Nausea & dyspepsia
  - Salivary hypersecretion & increased lacrimation
- **No deaths or treatment-related serious AEs**

# Hiccups Most Frequently Reported AEs in Long-term Studies

Preferred Term	NMS 1 mg N=915 n (%)	Placebo N=762 n (%)
Number of patients with at least 1 TEAE	725 (79.2)	459 (60.2)
Hiccups	397 (43.4)	56 (7.3)
Headache	162 (17.7)	99 (13.0)
Nausea	154 (16.8)	69 (9.1)
Throat irritation	149 (16.3)	61 (8.0)
Nasopharyngitis	118 (12.9)	66 (8.7)
Dyspepsia	115 (12.6)	45 (5.9)
Dizziness	85 (9.3)	53 (7.0)
Stomatitis	78 (8.5)	29 (3.8)
Salivary hypersecretion	69 (7.5)	21 (2.8)
Constipation	68 (7.4)	39 (5.1)
Oral discomfort	59 (6.4)	19 (2.5)
Hypertension	57 (6.2)	22 (2.9)
Dry mouth	52 (5.7)	34 (4.5)

# Discontinuation Rate Due to AEs Low in Long-term Studies

Preferred Term	NMS 1 mg N=915 n (%)	Placebo N=762 n (%)
Number of patients with at least 1 TEAE	52 (5.7)	28 (3.7)
Gastrointestinal disorders	29 (3.2)	13 (1.7)
Nausea	16 (1.7)	5 (0.7)
Oral discomfort	7 (0.8)	0
Vomiting	5 (0.5)	4 (0.5)
Stomatitis	4 (0.4)	1 (0.1)
Dry mouth	3 (0.3)	0
Dyspepsia	2 (0.2)	5 (0.7)
Diarrhea	2 (0.2)	3 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	22 (2.4)	4 (0.5)
Hiccups	9 (1.0)	0
Throat irritation	7 (0.8)	3 (0.4)
Throat tightness	3 (0.3)	0
Nervous system disorders	11 (1.2)	7 (0.9)
Dizziness	5 (0.5)	2 (0.3)
Headache	4 (0.4)	2 (0.3)
Psychiatric disorders	9 (1.0)	2 (0.3)
Depression	3 (0.3)	1 (0.1)
Vascular disorders	3 (0.3)	2 (0.3)
Hypertension	3 (0.3)	1 (0.1)

# Outline of Safety Review: Nicotine Mouth Spray

1. Safety experience of all Nicotine Replacement Therapy (NRT)
2. Clinical safety experience with Nicotine Mouth Spray (NMS)
- 3. Post-marketing safety experience with NMS (2011-2018)**
4. Specific safety considerations relevant to OTC use of NMS

# Post-marketing AE Reporting Rate is Low for NMS

- **4830 total cases**
  - 473 cases serious
- **Exposure**
  - 21.3 million dispensers
  - 3.2 billion sprays\*
- **1 fatal case reported – not related**
- **Sixteen cases reported in ages <18 years, none serious**

\*150 sprays per dispenser

# Frequent Adverse Events in Serious Cases Reflect Transferred Dependence

Serious Cases, Adverse Events PTs	Case Count
Drug dependence	264
Incorrect drug administration duration	132
Nicotine dependence	31
Overdose	24
Dyspnea	22
Dependence	17
Product quality issue	15
Drug ineffective	13
Intentional product use issue	11
Headache	11
Asthma	11
Hiccups	10
Pharyngeal edema	11
Throat irritation	10
Wrong technique in product usage process	10

## Dependence & Oral NRTs

- **Serious by convention**
- **Reported commonly with all oral OTC NRTs**
  - Not more frequent with NMS
- **No reports of dependence developing in nicotine naïve**
- **Transferred dependence**

# Most Commonly Reported Non-Serious AEs are Consistent with Those Seen in Clinical Development

Non-Serious Cases, Adverse Events PTs	Case Count
Hiccups	629
Oral discomfort	615
Nausea	519
Throat irritation	525
Drug ineffective	385
Vomiting	368
Product quality issue	311
Malaise	269
Dyspnoea	248
Burning sensation	193
Drug administration error	159
Cough	162
Dyspepsia	137
Wrong technique in product usage process	131
Dizziness	126
Oropharyngeal pain	122
Accidental exposure to product	115
Incorrect drug administration duration	118
Overdose	113
Retching	100
Tongue discomfort	101

# Outline of Safety Review: Nicotine Mouth Spray

1. Safety experience of all Nicotine Replacement Therapy (NRT)
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4. **Specific safety considerations relevant to OTC use of NMS**

# Safety of NRTs Varies Primarily in Local Reactions

- **Systemic effects of nicotine identified with NRT use**
  - Reported with all formulations
    - e.g. nausea, vomiting, headache, palpitations
    - Differences of local reactions expected due to route of administration
- **Adverse events associated with smoking cessation are commonly reported**
  - e.g. dysphoria, irritability, difficulty concentrating, dizziness, restlessness or impatience

OTC Dosage Forms	Local Reactions
Gum	Jaw tightness and jaw pain
Lozenge	Dyspepsia, burning sensation in mouth or throat
Nicotine mouth spray	Hiccups Mouth and throat irritation
Rx Dosage Forms	Local Reactions
Inhaler	Cough, Mouth and throat irritation
Nasal Spray	Sneezing, running nose, lacrimation, cough

# Abuse Definitions

- **Abuse definition in safety reporting:**
  - Abuse is explicitly stated by the reporter
  - Repeated use for a *non-therapeutic purpose* regardless of harm
  - Used to produce a euphoric effect
- **Abuse definition in our safety review:**
  - Term “drug abuse” or “substance abuse” reported
  - Term potentially associated with abuse such as “intentional product misuse” or “overdose” reported, and its narrative reported:
    - Non-therapeutic use
    - Use for a perceived reward
    - Use for “getting high”
  - Regardless of single, sporadic or persistent use

## **Abuse with OTC NRT is Low**

- **Abuse has been a topic of concern with prior US OTC oral NRT approvals**
- **Comprehensive program to monitor use in OTC setting**
- **No signal of abuse revealed**
- **2010 FDA review concluded that NRT products have a low potential for abuse\***

## Reporting Frequency of Abuse and Misuse has Been Very Low with NMS

- **No NMS cases reported the term abuse**
- **No overdose cases suggested the potential for abuse**
- **21 cases reported intentional product misuse, 20 were non-serious**
  - 2 cases: Intentional misuse suggested the potential of abuse
  - 1 case: Pharmacy employee tried and experienced asthma attack
  - Distribution of Intentional misuse cases by country:
    - Self-selection markets: Canada 7, Australia 4, France 4, Ireland 1, United Kingdom 1
    - Behind the counter: Germany 2, Greece 1, Iceland 1

# Accidental Exposure in Children with NMS

- **Child resistance testing**
  - Conducted and acceptable
- **2 reports**
  - accidental exposure to eye (non-serious)
- **No reports**
  - Self administering in infants/ small children ( $\leq 6$  years)



## NMS has a Favorable Safety Profile

- **Safety profile consistent with other forms of OTC NRT**
  - Local adverse events are similar to other oral NRTs
  - Hiccups, mouth and throat irritation most common AE's for NMS
  - Hiccups decrease over time
- **No evidence of abuse of NMS**
- **Overall safety**
  - Significant clinical safety experience with NMS
  - Significant post-marketing safety experience with NMS
- **Important new option for smokers seeking to quit**

# Consumer Studies

**Julie L. Aker, MT(ASCP)**

President & CEO

Concentrics Research

## **Consumers Have Self-Managed With OTC NRT Products for Over 20 Years**

- **NRT products available for 2 decades as OTCs**
- **Consumers know how to self-treat with NRTs**
- **Established FDA approved labeling exists for OTC NRT products**
- **The NMS label is comprised of information from the established NRT labeling**
- **We focused our program primarily on new information on the NMS labeling**

# NMS Labeling – DFL & QSG

## Drug Facts Label

### Outer Panel

**■ not for sale to those under 18 years of age**  
**■ proof of age required**  
**■ not for sale in vending machines or from any source where proof of age cannot be verified**

**LIFT  
HERE**

**For Complete  
Drug Facts Label**

**TAMPER EVIDENT FEATURE:** The spray container is protected in a clear plastic shell. Do not use if the sealed plastic shell is open or damaged. Retain this package for complete product information.

## Drug Facts

<b>Active ingredient (in each spray)</b>	<b>Purpose</b>
Nicotine 1 mg.....	Stop smoking aid

**Use**

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

**Warnings**

If you are pregnant or breast feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

**Ask a doctor before use if you have**

- heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate
- high blood pressure not controlled with medication. Nicotine can increase blood pressure
- stomach ulcer or diabetes
- history of seizures

**Ask a doctor or pharmacist before use if you are**

- using a non-nicotine stop smoking drug
- taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

**When using this product**

- hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.

**Stop use and ask a doctor if**

- mouth problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as heartburn, nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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**EAS  
TAGGED**

**Lot:**

**Exp:**

## Drug Facts Label and Quick Start Guide

### Inner Panels

**Usage Facts (continued)**

Keep out of reach of children and pets. Nicorette QuickMist Mouth Spray may have enough nicotine to make children and pets sick. In case of overdose, get medical help or contact a Poison Control Center right away.

**Directions**

- If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
- before using this product, read the enclosed User's Guide and Quick Start Guide for complete directions and other important information
- do not inhale when spraying
- for best results do not swallow for 2-3 seconds after spraying
- rise immediately with water if it sprays in eyes as irritation will occur
- to increase your chance of success it is important to use the nicotine mouth spray according to the following 12-week schedule:

**Step 1: Weeks 1-6**

- begin using the nicotine mouth spray on your quit day
- in the first 6 weeks, use the nicotine mouth spray as directed in the table below; however, do not exceed the maximum dose

Use	Max per hour	Max per day
1-2 sprays when you would normally smoke a cigarette or have a craving to smoke use the second spray if your cravings are not reduced within a few minutes)	4 sprays per hour	64 sprays per day

**Step 2: Weeks 7-9**

- start reducing the number of sprays per day
- by the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1

**Step 3: Weeks 10-12**

- continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12

- nicotine mouth spray is a medicine and must be used in a certain way to get the best results. It is important to complete treatment. If you feel you need to use the Nicorette QuickMist Mouth Spray for a longer period to keep from smoking, talk to your health care provider.

**Other information** → do not store above 25°C (77°F)

**Inactive ingredients** acessulfame potassium, dehydrated alcohol, glycerin, hydrochloric acid, menthol, mint flavor, poloxamer 407, propylene glycol, purified water, sodium bicarbonate, sucralose, tromethamine

**Questions or comments?** 1-800-XXX-XXXX

Distributed by:  
**GSK Consumer Healthcare**  
Warren, NJ 07059

Made in XXXXXX

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**TO INCREASE YOUR SUCCESS IN QUITTING**

1. You must be motivated to quit.
2. Use enough Nicorette QuickMist Mouth Spray each day to reduce your urge to smoke.
3. Use for the entire 12-week program.
4. Use with the MyQuit Behavioral Support Program as directed in the enclosed User's Guide.

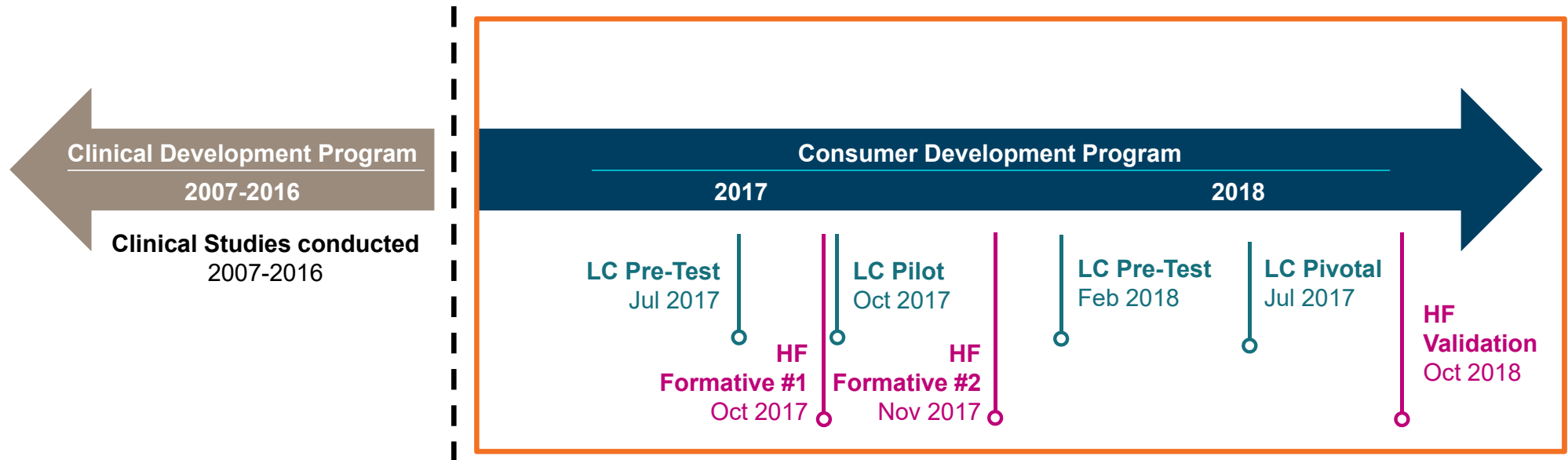
For more information and for a **FREE** individualized stop smoking program, please visit [www.Nicorette.com](http://www.Nicorette.com) or see inside for more details.

# NMS Labeling – User Guide



How the Mouth Spray Works	4
Following the 3-Step Plan	12
Planning for Success	18
Behavioral Support Program (MyQuit)	24
Managing for Success	28

# Consumer Development Plan



HF: Human Factors  
LC: Label Comprehension

# Outline of Consumer Studies Review

- 1. Label Comprehension**
2. Human Factors

# Label Comprehension Methods

- **Purpose: To evaluate if the labeling is clear**
- **FDA Guidance for Label Comprehension Studies for Nonprescription Drug Products**
- **Interview only; no drug administered**
- **1:1 interviews**
- **Questions are posed in 3rd-party scenarios**

## Scenario Example

- **Sandy has been using this product for 9 weeks**
- **In Step 1, she was using about 10 sprays per day**
- **According to the label, how many sprays per day should Sandy be using by the end of week 9?**

# Drug Facts Label

■ not for sale to those under 18 years of age  
 ■ proof of age required  
 ■ not for sale in vending machines or from any source where proof of age cannot be verified

**TAMPER EVIDENT FEATURE:** The spray container is protected in a clear plastic shell. Do not use if the sealed plastic shell is open or damaged.

Retain this package for complete product information.

**LIFT  
HERE** ➔

**For Complete  
Drug Facts Label**

**Drug Facts**

Active ingredient (in each spray)	Purpose
Nicotine 1 mg	Stop smoking aid

**Use**

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

**Warnings**

If you are pregnant or breast feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

**Ask a doctor before use if you have**

- heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate
- high blood pressure not controlled with medication. Nicotine can increase blood pressure
- stomach ulcer or diabetes
- history of seizures

**Ask a doctor or pharmacist before use if you are**


- using a non-nicotine stop smoking drug
- taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

**When using this product**

- hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.


**Stop use and ask a doctor if**

- mouth problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as heartburn, nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)



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EAS  
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Lot: XXXXXXXXXX

Exp: XXXXXXXXXX

**Drug Facts (continued)**

Keep out of reach of children and pets. Nicorette QuickMist Mouth Spray may have enough nicotine to make children and pets sick. In case of overdose, get medical help or contact a Poison Control Center right away.

**Directions**

- If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
- before using this product, read the enclosed User's Guide and Quick Start Guide for complete directions and other important information
- do not inhale when spraying
- for best results do not swallow for 2-3 seconds after spraying
- rinse immediately with water if you spray in eyes as irritation will occur
- to increase your chance of success it is important to use the nicotine mouth spray according to the following 12-week schedule:

Step 1: Weeks 1-6								
<ul style="list-style-type: none"> <li>begin using the nicotine mouth spray on your quit day</li> <li>in the first 6 weeks, use the nicotine mouth spray as directed in the table below; however, do not exceed the maximum dose</li> </ul>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="text-align: left; padding: 2px;">Use</th> <th style="text-align: center; padding: 2px;">Max per hour</th> <th style="text-align: center; padding: 2px;">Max per day</th> </tr> <tr> <td style="padding: 2px;">1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)</td> <td style="text-align: center; padding: 2px;">4 sprays per hour</td> <td style="text-align: center; padding: 2px;">64 sprays per day</td> </tr> </table>	Use	Max per hour	Max per day	1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	4 sprays per hour	64 sprays per day	
Use	Max per hour	Max per day						
1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	4 sprays per hour	64 sprays per day						

Step 2: Weeks 7-9
<ul style="list-style-type: none"> <li>start reducing the number of sprays per day</li> <li>by the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1</li> </ul>

Step 3: Weeks 10-12
<ul style="list-style-type: none"> <li>continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12</li> </ul>

• nicotine mouth spray is a medicine and must be used in a certain way to get the best results.  
 • it is important to complete treatment. If you feel you need to use the Nicorette QuickMist Mouth Spray for a longer period to keep from smoking, talk to your health care provider.

**Other information** • do not store above 25°C (77°F)

**Inactive ingredients** acesulfame potassium, dehydrated alcohol, glycerin, hydrochloric acid, menthol, mint flavor, poloxamer 407, propylene glycol, purified water, sodium bicarbonate, sucralose, tromethamine

**Questions or comments?** 1-800-xxx-xxxx

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# Label Comprehension Study Design

- **The pivotal study was conducted in 504 subjects**
  - Smokers, ages 18 and older
  - 26% of the population was of limited literacy
- **Participants provided 2 responses:**
  - Initial response to answer the question
  - Follow-up response with their rationale
- **Both responses are reviewed and coded to determine “correct,” “acceptable,” or “incorrect”**
- ***A priori* thresholds were established for primary endpoints**

# Comprehension – Four Primary Endpoints

## Pivotal Label Comprehension Results

		Total Population N=504	
Question #	Primary Endpoint	n	% (95% CI)
Q9	Directions: Step 1 – Maximum number of sprays per hour – 4 sprays per hour	463	91.9 (89.1, 94.1)
Q13	Directions: Do not inhale when spraying	462	91.7 (88.9, 93.9)
Q11	Directions: Step 1 – Maximum number of sprays per day – 64 sprays per day	451	89.5 (86.5, 92.0)
Q17	Directions: Rinse immediately with water if you spray in eyes as irritation will occur	392	77.8 (73.9, 81.3)

**Within the total population (N=504), the primary communication objectives met or nearly met the 80% LB threshold**

# Comprehension: Eight Secondary Endpoints

## Overall Correct Responses Demonstrating Comprehension

Question #	Secondary Endpoint	Total Population N=504		
		n	%	95% CI
Q18	Directions: To increase your chance of success it is important to use the nicotine mouth spray according to following the 12-week schedule	484	96.0	(93.9, 97.6)
Q16	Directions: Step 2 – Start reducing the number of sprays per day	476	94.4	(92.1, 96.3)
Q15	Directions: For best results do not swallow for 2-3 seconds after spraying	472	93.7	(91.2, 95.6)
Q14	Directions: Step 1 – Use 1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	469	93.1	(90.5, 95.1)
Q7	Directions: Step 1 – Use 1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	444	88.1	(84.9, 90.8)
Q8	Directions: Step 2 – By the end of week 9 you should be using HALF of the average number of sprays per day that you used in Step 1	415	82.3	(78.7, 85.6)
Q12	When using this product: Hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment	409	81.2	(77.5, 84.5)
Q10	Directions: Step 3 – Continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12	338	67.1	(62.8, 71.2)

# Consumer Studies Summary

- **Label Comprehension**

- Consumers demonstrated comprehension of the Drug Facts Label

- **Human Factors**

- Consumers demonstrated proper use the of the device
- Consumers comprehended key written behavioral support messages

# Sponsor Summary

**Sue James**

Vice-President, Head Global Regulatory Affairs

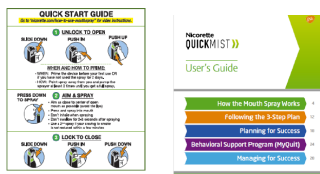
# The Benefits of NMS are Well Supported

- **Benefits**

- Innovative format provides faster absorption and flexible dosing
- New product launches create new/renewed interest in quitting
- Doubles quit rates vs placebo
- Data firmly supports label claims

<i><b>Drug Facts</b></i>	
<i><b>Active ingredient (in each spray)</b></i>	<i><b>Purpose</b></i>
Nicotine 1 mg .....	Stop smoking aid
<i><b>Use</b></i>	
• reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking	

# Comprehensive Consumer Support



**With NMS**

**Clear, engaging  
user-friendly  
self-help materials**



**On The Web**

**Helpful tips &  
advice on Quit.com  
support hub**



**On The Go**

**Log cravings &  
track progress  
via MyQuit  
mobile app**



**To Your Inbox**

**Motivation  
via daily emails  
from our customized  
email program**

# Every Quit Matters.....

- **Many smokers will need to make multiple attempts to quit before succeeding**
- **FDA's motivational campaign "Every try counts" acknowledges the hardship of quitting and the importance to keep trying with messages:**
  - Quitting smoking takes practice
  - You learn something every time you try to quit
  - You haven't failed if you keep trying



## The Risks of NMS are Well-Characterized

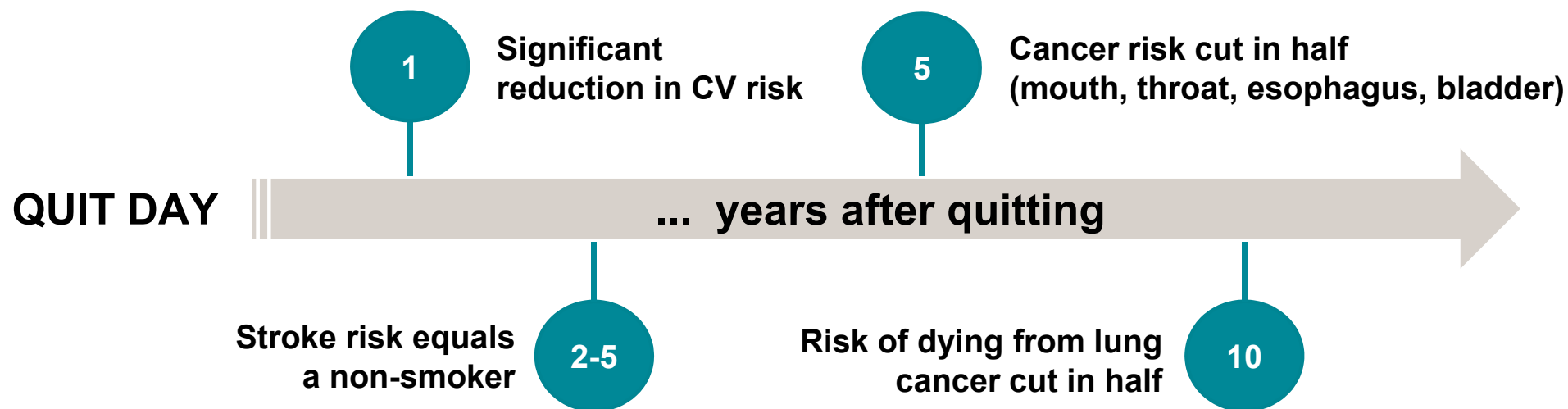
- **Risks - comparable to current OTC NRT products**
  - Safety profile of NRT well established over 2 decades OTC
  - 7 years of NMS global marketing experience
  - NMS safety is consistent with known NRT profiles
  - No new safety signals identified
  - Abuse potential considered to be low
- **Promotion to adult smokers only**
- **Pharmacovigilance and Quarterly Safety Reporting**

## **Continued Smoking Poses Significant Public Health Risks**

- **Cigarette smoking causes ~ 500,000 deaths each year**
- **Smoking causes 90% of all lung cancer deaths**
- **Smoking causes 80% of all deaths from COPD**
- **Smoking increases risk of coronary heart disease 2 to 4 times**
- **Smoking increases risk of developing lung cancer by 25 times**

# Quitting Smoking Delivers Significant Health Benefits

## Health Benefits After Quitting.....



## NMS Addresses Call to Action for NRT Innovation

- ***“As a public health agency, there is no greater impact we can have to improve the health of our nation than to significantly reduce the rate of tobacco-related disease and death.”***
- ***“The development of novel NRT products, regulated as new drugs, is a critical part of our overall strategy on nicotine.”***
- ***“Use of FDA-approved NRT products is generally considered to double the likelihood of a successful quit attempt (with variations between products).”***

# **NMS is an Important New Therapeutic Option**

- **Comprehensive program and aligned with current 2019 FDA guidance**
- **Doubles the rate of quitting compared to placebo**
- **Well-known and favorable safety profile**
- **Extensive global marketing experience**
- **Provides smokers with a novel, differentiated format to help them in their efforts to quit**

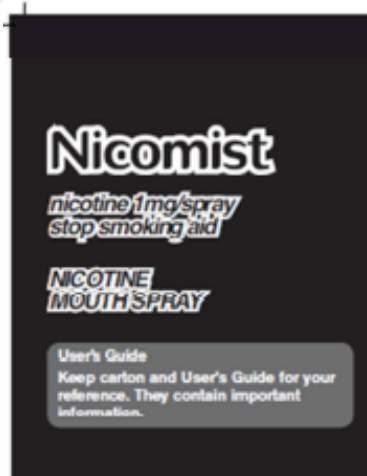
# Backup Slides Shown



# Design of the Naturalistic Efficacy Study 38: Recruitment and Inclusion/Exclusion

Design Element	Characteristics
Recruitment	Advertisements (mailed postcards, newspaper ads, radio/television/internet broadcast ads)
Screening	<ul style="list-style-type: none"><li>• Standard screening questionnaire and script</li><li>• Baseline visit scheduled for those qualified</li></ul>
Inclusion / Exclusion Criteria	<ul style="list-style-type: none"><li>• Current daily smoker</li><li>• Motivated to quit with NRT</li><li>• Willing to use only study product for study duration</li><li>• Negative urine drug screen at baseline</li><li>• Not previously randomized to use investigational product in another study</li></ul>

# Original User Guide – Page 1



Always follow the instructions below when using the Nicomist Mouth Spray. If you are not sure how to use the product, check with your doctor or pharmacist. If you are not sure how to open the spray pump, check with your pharmacist.

#### How to open the spray pump

1. Use your thumb to slide down the button (a) until it can be pushed **lightly** inwards (b). Do not push too hard.
2. While pushing in, slide upwards (c) to unlock the top of the spray pump. Release the button.

#### TO UNLOCK NOZZLE



#### How to prime the spray pump

When you use the spray for the first time you must first prime the spray pump. Open the spray pump as described above, then point the spray safely away from you and any other adults, children or pets near you. Press the top of the spray pump with your index finger. Press several times until a fine spray appears. If you do not use the spray for 2 days, this priming procedure will have to be repeated.

#### How to use the spray

1. Point the spray nozzle towards your open mouth and hold the spray as close to your mouth as possible.
2. Press the top of the spray pump **firmly** to release one spray into your mouth, **avoiding the lips**. Do not inhale while spraying to avoid getting the spray down your throat. For best result, do not swallow for 2-3 seconds after spraying.



#### How to close the spray pump

1. Slide the button down (d) until it can be pushed **lightly** inwards (e).
2. While pushing in, slide the spray pump downwards (f). Release the button. The spray pump is now closed.



#### TO RETRACT NOZZLE



Close the spray **every** time after use to prevent accidental spraying and use of the spray by children. To take another dose, repeat the steps above.

#### PLANNING YOUR SUCCESS.

- 1) The key to accomplishing anything important is commitment. When it comes to quitting smoking, that is especially true. **Nicomist Mouth Spray** can help if you really want to quit. **Nicomist Mouth Spray** helps reduce withdrawal symptoms including urges to smoke associated with quitting smoking.
- 2) Begin using the **Nicomist Mouth Spray** on your quit day.
- 3) This User's Guide outlines a 12-week plan for **Nicomist Mouth Spray**. Even though you may feel confident about your non-smoking status after a few weeks, it's important to stick with the plan to help you remain smoke free.
- 4) Your chances of staying off cigarettes are much better if you use enough **Nicomist Mouth Spray**, especially during the first six weeks. Remember to use 1 to 2 sprays when you would have normally smoked a cigarette. For example, if you smoked 20 cigarettes per day before you quit, you should use at least 20 sprays per day.
- 5) It is important to complete treatment. If you feel you need to use **Nicomist Mouth Spray** for a longer period to keep you from smoking, talk to your health care provider.
- 6) If you have questions about using **Nicomist Mouth Spray**, see informed consent or alert card for contact information.

#### YES! YOU WANT TO QUIT.

Wonderful. You've made the most important

decision of all, to stop smoking. And by choosing **Nicomist Mouth Spray** to help you, you're starting on the right path. Now remember, improving your chances for success in stopping smoking doesn't mean just using the **Nicomist Mouth Spray**. It means setting up and following a program like the one we suggest in this User's Guide. Your own success depends on your effort, your level of addiction to tobacco, and your commitment to following your program.

#### GET MOTIVATED. STAY MOTIVATED.

Everyone has a reason for quitting—whether you're concerned about your health, your appearance, family or peer pressure, or the effect of secondhand smoke on your loved ones—all of the above, or something else entirely. Whatever your reasons, write them down. There's a section at the end of this User's Guide to write down your most important reasons to quit smoking. Referring back to what has motivated your taking steps to stop smoking can help you focus on your reasons for quitting. Lots of people quit with a co-worker, spouse or friend and use them as a quitting buddy. You can help each other out by providing extra encouragement in tough moments.

#### YOU'RE READY TO START.

Okay, you're ready. Now before you do anything else, you have a bit of planning to do. Read this User's Guide all the way through. Next, plan your quitting schedule. Get a calendar to follow your progress and mark the following four important dates.

**Step I** - The day you start using the **Nicomist Mouth Spray**.

**Step II** - Beginning of Week 7 when you start reducing the number of sprays per day.

**Step III** - Beginning of Week 10 when you continue reducing the number of sprays per day.

**Finish Program** - End of Week 12 when you stop using the spray.

Next, let's review these important warnings that are also listed on the back of the carton within the **Drug Facts**:

# DFL Used in Naturalistic Study



**Nicomist**  
nicotine 1mg/spray  
stop smoking aid

**NICOTINE  
MOUTH SPRAY**

**1  
mg**

**140 SPRAYS, 1mg/SPRAY**  
Alcohol 10%

**Other information**  
• Do not store above 25°C (77°F)

**Inactive ingredients**  
acesulfame potassium, dehydrated alcohol, glycerin, hydrochloric acid, menthol, mint flavor, poloxamer 407, propylene glycol, purified water, sodium bicarbonate, sucralose, tromethamine. May contain capsaicin.

**Questions or comments?**  
See informed consent or alert card for contact information

■ not for sale to those under 18 years of age  
■ proof of age required  
■ not for sale in vending machines or from any source where proof of age cannot be verified

**TO INCREASE YOUR SUCCESS IN QUITTING:**

1. You must be motivated to quit.
2. **Use Enough, especially during the first six weeks** – Use 1-2 sprays when you would have normally smoked a cigarette. For example if you smoked 20 cigarettes per day before you quit, you should use at least 20 sprays per day.
3. **Use Long Enough** – Use nicotine mouth spray for the full 12 weeks.
4. **Use with a support program** as directed in the enclosed User's Guide.

**Distributed by:**  
McNeil Consumer Healthcare,  
Division of McNeil - PPC, Inc.

**Caution:**  
New Drug - Limited by  
United States laws to  
investigational use

**Drug Facts**

Active ingredient (in each spray)	Purpose
Nicotine 1mg.....	Stop smoking aid

**Use** • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

**Warnings**  
If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

**Ask a doctor before use if you have**

- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase blood pressure.
- stomach ulcer or diabetes

**Ask a doctor or pharmacist before use if you are**

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

**When using this product**

- hiccups or minor mouth and throat irritation may occur
- be careful not to spray in eyes as irritation will occur. Rinse immediately with water.

**Stop use and ask a doctor if**

- mouth problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

**Keep out of reach of children and pets.** Nicotine mouth spray may have enough nicotine to make children and pets sick. In case of overdose, get medical help or contact a Poison Control Center right away.

**Directions**

- if you are under 18 years of age, ask a doctor before use
- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the mouth spray on your quit day
- use according to the following schedule:

Step I Weeks 1-6
<ul style="list-style-type: none"> <li>• 1-2 sprays when you would normally smoke a cigarette or have urges to smoke (use the second spray if your urges are not reduced within a few minutes).</li> <li>• for many smokers this means about 1-2 sprays every 30 minutes to 1 hour</li> </ul>
Step II Weeks 7-9
<ul style="list-style-type: none"> <li>• start reducing the number of sprays per day</li> <li>• by the end of week 9 you should be using HALF the average number of sprays per day that you used in Step I</li> </ul>
Step III Weeks 10-12
<ul style="list-style-type: none"> <li>• continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12</li> </ul>

- do not use more than 4 sprays per hour
- do not use more than 64 sprays per day
- for best results do not swallow for 2-3 seconds after spraying
- it is important to complete treatment. If you feel you need to use the Nicomist Mouth Spray for a longer period to keep from smoking, talk to your health care provider

# DFL and QSG Tested in LCS and HF Summative

- not for sale to those under 18 years of age
- proof of age required
- not for sale in vending machines or from any source where proof of age cannot be verified

**TAMPER EVIDENT FEATURE:** The spray container is protected in a clear plastic shell. Do not use if the sealed plastic shell is open or damaged.

Retain this package for complete product information.

## Drug Facts

### Active ingredient (in each spray)

Nicotine 1 mg Purpose  
Stop smoking aid

### Use

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

### Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

### Ask a doctor before use if you have

- heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes
- history of seizures

### Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

### When using this product

- hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.

### Stop use and ask a doctor if

- mouth problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as heartburn, nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)



EAS  
TAGGED



Lot:

Exp:

**LIFT  
HERE**  
For Complete  
Drug Facts Label

## Drug Facts (continued)

Keep out of reach of children and pets. Nicorette QuickMist Mouth Spray may have enough nicotine to make children and pets sick. In case of overdose, get medical help or contact a Poison Control Center right away.

## Directions

- If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
- before using this product, read the enclosed User's Guide and Quick Start Guide for complete directions and other important information
- do not inhale when spraying
- for best results do not swallow for 2-3 seconds after spraying
- do not eat or drink for 15 minutes before using this spray or while using the spray
- rinse immediately with water if you spray in eyes as irritation will occur
- to increase your chance of success it is important to use the nicotine mouth spray according to the following 12-week schedule:

### Step 1: Weeks 1-6

- begin using the nicotine mouth spray on your quit day
- in the first 6 weeks, use the nicotine mouth spray as directed in the table below; however, do not exceed the maximum dose

Use	Max per hour	Max per day
1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	4 sprays per hour	64 sprays per day

### Step 2: Weeks 7-9

- start reducing the number of sprays per day
- by the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1

### Step 3: Weeks 10-12

- continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12

- nicotine mouth spray is a medicine and must be used in a certain way to get the best results
- it is important to complete treatment. If you feel you need to use the Nicorette QuickMist Mouth Spray for a longer period to keep from smoking, talk to your health care provider.

**Other information** • store at 20 - 25°C (68 - 77°F). Avoid excessive heat above 30°C (86°F).

**Inactive ingredients** acesulfame potassium, dehydrated alcohol, glycerin, hydrochloric acid, menthol, mint flavor, poloxamer 407, propylene glycol, purified water, sodium bicarbonate, sucralose, tromethamine

**Questions or comments?** 1-800-xxx-xxxx

Distributed by:  
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## TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. Use enough Nicorette QuickMist Mouth Spray each day to reduce your urge to smoke.
3. Use for the entire 12-week program.
4. Use with the MyQuit Behavioral Support Program as directed in the enclosed User's Guide.

For more information and for a FREE individualized stop smoking program, please visit [www.Nicorette.com](http://www.Nicorette.com) or see inside for more details.

## QUICK START GUIDE

Go to "[nicorette.com/how-to-use-mouthspray](http://nicorette.com/how-to-use-mouthspray)" for video instructions.



### WHEN AND HOW TO PRIME:

- WHEN: Prime the device before your first use OR if you have not used the spray for 2 days.
- HOW: Point spray away from you and pump the sprayer at least 3 times until you get a full spray.

### PRESS DOWN TO SPRAY



### 2 AIM & SPRAY

- Aim as close to center of open mouth as possible (avoid the lips)
- Press and spray into mouth
- Don't inhale when spraying
- Don't swallow for 2-3 seconds after spraying
- Use a 2<sup>nd</sup> spray if your craving to smoke is not reduced within a few minutes



SEAL AREA

# Label Comprehension – Additional Qualitative Questions

- “How many cigarettes do you smoke daily?”. (Q.19)
  - Less than 1 cigarette per day (1.8%)
  - 1-5 cigarettes per day (22.4%)
  - 6-10 cigarettes per day (31.0%)
  - 11-15 cigarettes per day (16.1%)
  - 16-20 cigarettes per day (21.2%)
  - More than a pack per day (7.3%)
  - Don’t know (0.2%)
- “Have you attempted to quit smoking in the past?”. (Q.20)
  - Yes (80.0%)
  - No (19.8%)
  - Don’t Know (0.2%)
- IF YES AT Q20 “How many times have you attempted to quit smoking?”. (Q.21)
  - Once (13.9%)
  - Two or three (37.2%)
  - Three or four (20.3%)
  - Five or more (28.5%)

# Label Comprehension – Additional Qualitative Questions

- IF ‘OPENED DFL FLAP AT Q1’ ASK: “I see that you opened the flap. What led you to open the flap?”. (Q.23) – multiple responses were allowed
  - Yellow label/arrow/says flip open/saw flap/says additional information (57.8%)
  - Wanted to get more information/not enough information on the outside (52.9%)
  - Familiar with these flaps/usual place for more information (5.7%)
  - It was not sealed shut (5.2%)
- IF ‘ASKED IF THEY COULD OPEN THE FLAP AT Q1’ ASK: “You asked during the interview if you could open the flap. Why did you not open the flap when you were initially reading the label?”. (Q.24) – multiple responses were allowed
  - Was not sure you wanted me to open it (50.0%)
  - Thought it was sealed/didn’t want to damage it (15.6%)
  - Didn’t notice it/didn’t read completely (12.5%)
  - Wanted to open product first/read the outside first (9.4%)
  - Needed to open it/right thing to do (6.3%)
  - Just to make sure (6.3%)

# Label Comprehension – Additional Qualitative Questions

- IF YES AT Q20 “What methods have you tried to quit smoking in the past?”. (Q.22) – multiple responses were allowed
  - Cold Turkey (61.3%)
  - Nicotine patch (34.7%)
  - Nicotine gum (29.5%)
  - Vaping/e-cigarettes (15.4%)
  - Prescription non-nicotine medications (e.g. Chantix) (14.1%)
  - Sunflowers/candy/chewing gum, toothpicks/straws/fruit (7.9%)
  - Reducing/cutting back (6.9%)
  - Nicotine lozenge (5.5%)
  - Willpower/just stopped (5.5%)
  - Behavior therapy/thought control/modified routine/avoidance (5.0%)

# DFL Font Characteristics

## Drug Facts Label Outer Panel

**Font Size**

8 pt

7 pt

10 pt

6-8 pt

8 pt

6 pt

The outer panel includes a red warning box with 8 pt text, a yellow lift flap with 13 pt and 10 pt text, and a white box with 6-8 pt and 8 pt text. At the bottom, there is a barcode with 6 pt text and a lot/expiration date box with 8 pt text.

**Font Size**

13 pt

10 pt

## Drug Facts Label Inner Panel

**Font Size**

8 pt

6 pt

8 pt

6 pt

6-8 pt

The inner panel contains detailed drug facts, directions, and other information. It includes a table for dosing instructions (Step 1: Weeks 1-6, Step 2: Weeks 7-9, Step 3: Weeks 10-12) with 6 pt and 8 pt text. At the bottom, there is a barcode with 6 pt text and a lot/expiration date box with 8 pt text.

**Font Size**

13 pt

10 pt

Helvetica font used on label; lift flap in Arial font

# Criteria for Inclusion: Human Factors Study

- **User Group 1: (n=19)**
  - Male or female, of any race
  - 18-54 years of age
  - Currently smoke or are trying to quit smoking
  - Able to speak, read and understand English sufficiently to understand the nature of the study procedures
  - Reads and signs the Confidentiality/Disclosure Agreement (CDA) and Agreement to Participate (ATP)
- **User Group 2: (n=20)**
  - Male or female, of any race
  - 55 years of age and older
  - Currently smoke or are trying to quit smoking
  - Able to speak, read and understand English sufficiently to understand the nature of the study procedures
  - Reads and signs the CDA and ATP

# Label Comprehension Study

## Q13: Inhalation

13a) According to the label, is it okay or not okay to inhale when spraying this product?

**DO NOT READ LIST. SELECT ONE RESPONSE.**

	OKAY	1
	NOT OKAY	2
	DON'T KNOW	3
	OTHER (SPECIFY)	4

13b) Why do you say that?

# Examples of Dual Use in NRT Studies: Open-Label Lozenge and Gum

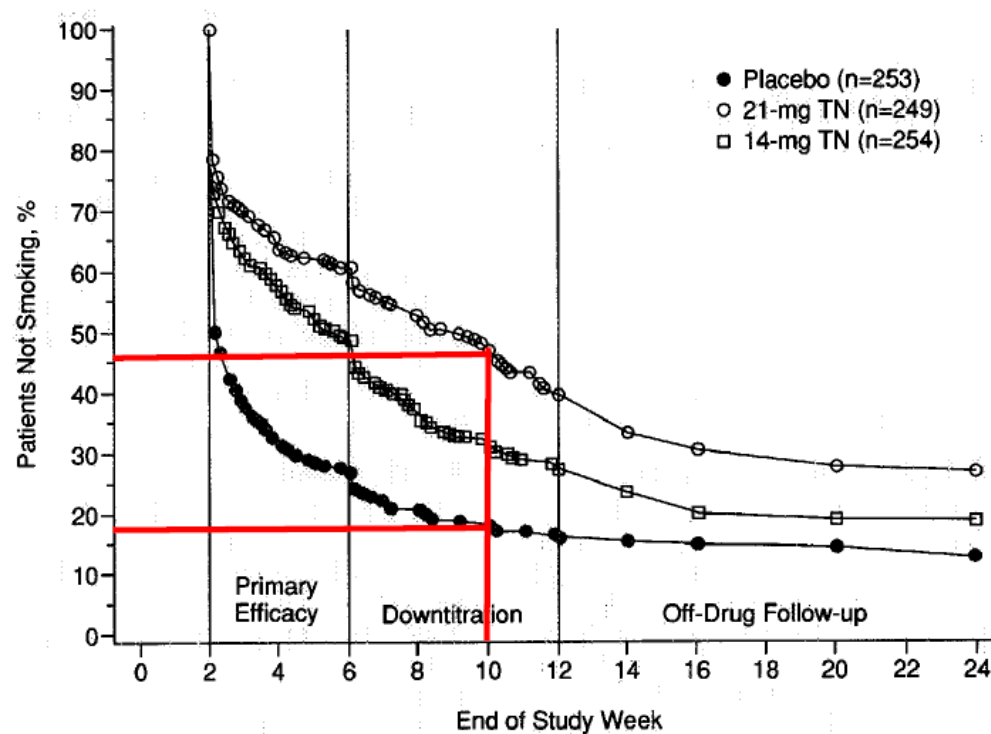
## Smoking at Week 2 in Open-Label Safety Study

	Lozenge N=447	Gum N=454
Still smoking	91%	95%

- Adult smokers with heart disease, uncontrolled hypertension, and/or diabetes
- Randomized 1:1 to lozenge or gum

**In addition, at week 12, most subjects still using 3 or 4 units of NRT  
(vs. mean of 5-6 units during the first 6 weeks)**

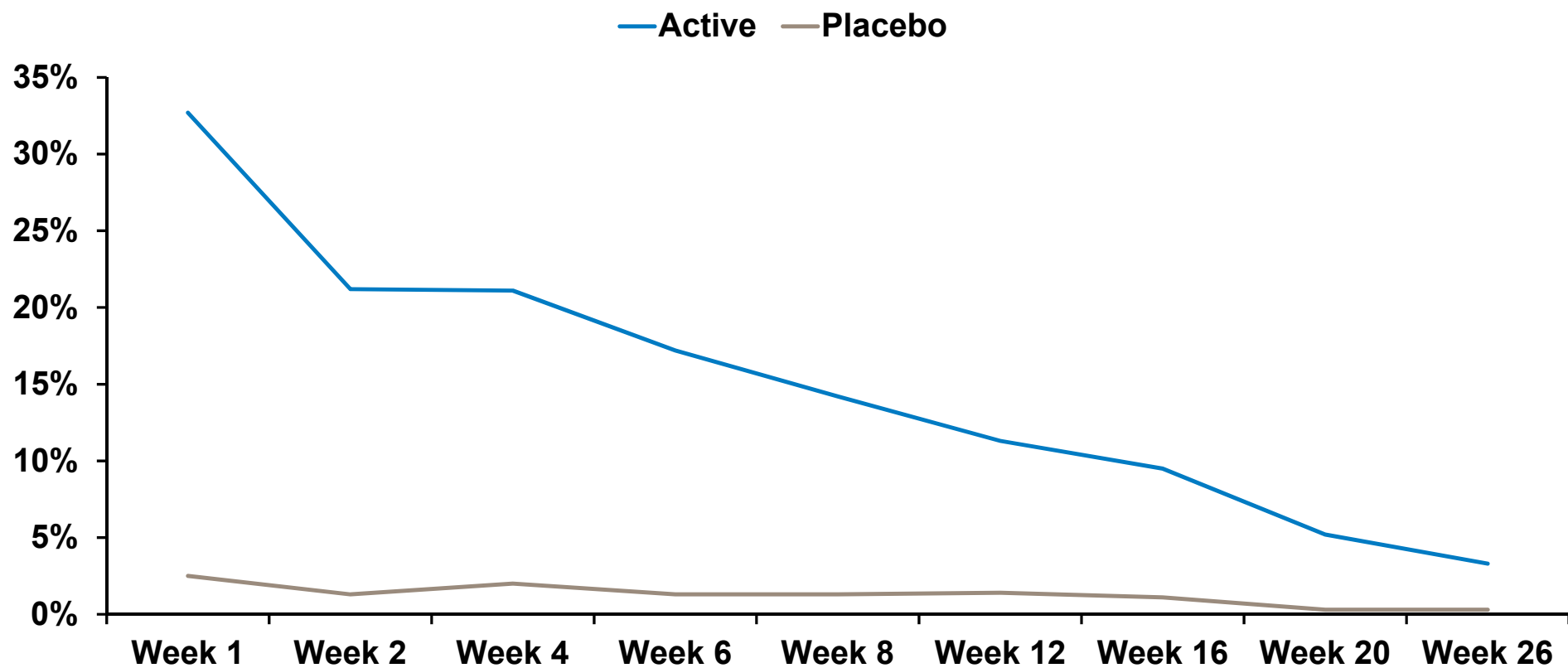
# Time to Smoking for the Pooled Database



Double-blind, randomized trial of nicotine patch vs. placebo

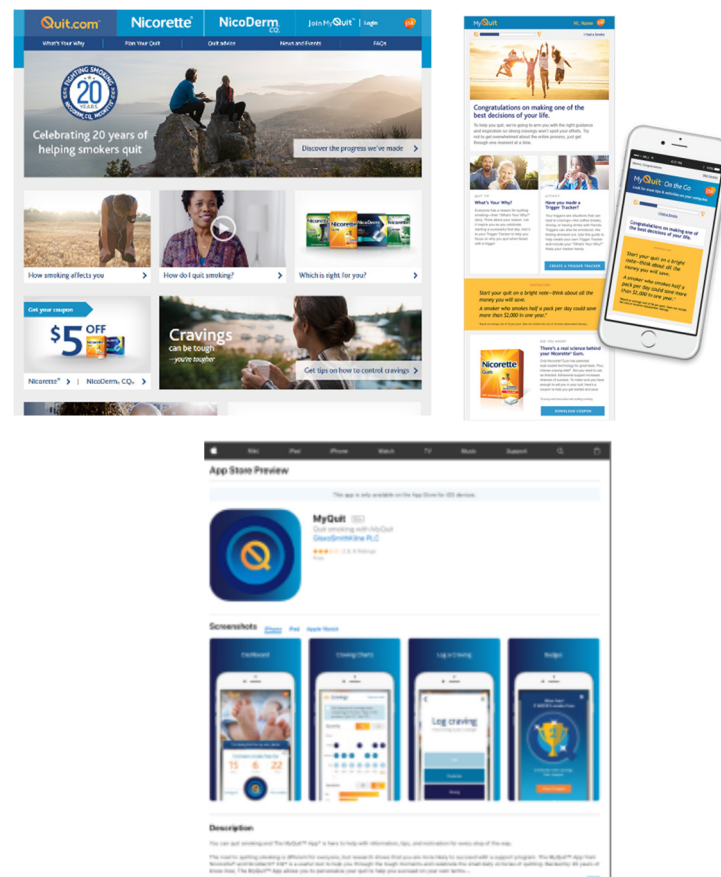
# Hiccups Over Time

## Study 38



# Strong Consumer Engagement with The MyQuit™ Behavioral Support Program Tools

- **1MM+ users visit Quit.com annually**
- **300,000+ MyQuit™ e-mail program participants since launch**
  - Clear evidence that program fosters more engaged quit attempts & improved adherence to therapy
- **6600+ MyQuit™ app downloads**



# Ethanol

- **The amount of ethanol per spray dose corresponds to 7.1 mg, i.e. 0.009 ml pure ethanol**
- **At maximum recommended usage of the spray, 64 doses per day, the subjects would ingest ethanol corresponding to 4.9 ml of wine (less than one teaspoon of wine with 12% alcohol content)**
- **To inform consumers, the product is clearly labelled with the ethanol content**

# Summary of Median NMS Sprays per Day Through Week 12

## Pivotal Efficacy Studies 11 and 38

Week	Median <sup>a</sup> Number of Spray Doses Standard Efficacy Study 11				Median <sup>b</sup> Number of Spray Doses Naturalistic Efficacy Study 38			
	NMS/ FAS <sup>c</sup>	Placebo/ FAS <sup>c</sup>	NMS/ Abstinent <sup>d</sup>	Placebo/ Abstinent <sup>d</sup>	NMS/ FAS <sup>c</sup>	Placebo/ FAS <sup>c</sup>	NMS/ Abstinent <sup>d</sup>	Placebo/ Abstinent <sup>d</sup>
1	13.1	18.2	14.6	19.1	10.4	13.5	10.8	13.9
2	14.2	18.8	13.1	17.9	9.9	12.5	10.6	8.4
4	11.6	12.6	9.6	8.6	9.0	11.3	6.8	7.1
6	10.2	11.0	6.6	7.8	8.8	10.9	5.5	4.4
8	8.3	8.4	6.3	5.6	7.9	10.2	4.4	3.7
12	4.3	3.9	3.3	0.3	5.9	8.6	3.4	3.2

a For each given period based on average daily doses for subjects reporting data for ≥50% of the days in that specific period.

b For each given period based on average daily doses for subjects reporting use data (excluding data of questionable validity) for ≥4 of the days in that week.

c Subjects in full analysis set.

d Subjects verified abstinent by week. For each period, summary statistics are based on available data from all subjects verified abstinent during that specific period.

FAS = full analysis set. NMS = nicotine mouth spray.